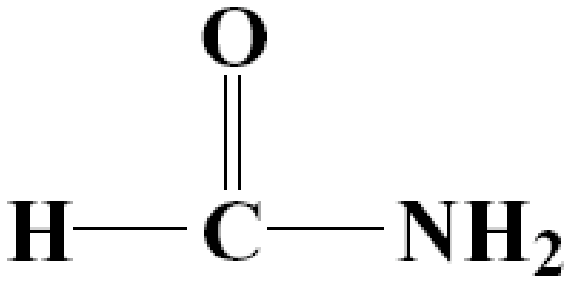
NTP
National Toxicology Program

Toxicology and carcinogenesis studies of formamide



Nomination

- Potential for significant human occupational exposure associated with wide use in manufacturing; classified as HPV by EPA
- Reproductive toxicity, genotoxicity, and carcinogenic potential because of inadequate data for regulatory purposes

Route of administration

Human exposure occurs by dermal and inhalation routes

- Inhalation: low vapor pressure of formamide prevented generation of high enough vapor concentrations
- Dermal: water best solvent but aqueous solutions not suitable for dermal application
- Diet: formamide not stable in feed
- Drinking water: aqueous formamide solutions not palatable

- Gavage in water

Three month studies: rats and mice

- Doses based on results of 12-day preliminary studies
- Rats and mice: 10, 20, 40, 80, 160 mg/kg + vehicle (water) control
- Five additional animals per group for formamide plasma concentrations

Three month study results: rats

- No mortality
- Mean body weights and body weight gain of males and females receiving 80 or 160mg/kg significantly reduced
- Dose related increase in the erythron (Hct, Hb, RBC) on days 23 and week 14 in 80 and 160mg/kg groups
- Degeneration of the testes and epididymis at 160mg/kg
- Plasma formamide concentrations increased linearly with dose with no indication of saturation

Two year study results: rats

- Survival of both sexes comparable to control
- Mean body weights of 80mg/kg groups lower than controls
- No treatment related neoplastic lesions
- Bone marrow hyperplasia increased in 80mg/kg males

Three month study results: mice

- No mortality
- Significant reduction of mean body weight and body weight gain of males receiving 80 or 160 mg/kg
- Males:
  - -Increased incidence of abnormal residual bodies of the testis in 160 mg/kg group
  - -Increased incidences of hyperplasia and chronic active inflammation of the pancreatic duct in 160mg/kg group
- Females:
  - -Increased incidences of hyperplasia, cytoplasmic alteration, and chronic active inflammation of the pancreatic duct in the 160mg/kg group
- Plasma formamide concentrations increased linearly with dose with no indication of saturation

Two year study results: mice

- Survival of both sexes comparable to control
- Mean body weights of 80mg/kg groups lower than control during most of the study

Neoplasms of the liver in mice

	Control	20mg/kg	40mg/kg	80mg/kg
Male Hemangiosarcoma	1/50	5/50	7/50*	8/50*
Female Adenoma or carcinoma	9/50	15/50	13/50	18/50*

*$p \leq 0.05$

Treatment related non-neoplastic lesions in mice

- Male
  - testes: mineralization of the testicular artery and tunic
  - spleen: hematopoietic cell proliferation

Conclusions

- Male rats: no evidence of carcinogenic activity
- Female rats: no evidence of carcinogenic activity
- Male mice: clear evidence of carcinogenic activity based on increased incidences of hepatic hemangiosarcomas
- Female mice: equivocal evidence of carcinogenic activity based on increased incidence of hepatocellular adenoma or carcinoma
- Mineralization of the testicular arteries and tunic and hematopoietic cell proliferation of the spleen in male mice